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^{119}Sn Mössbauer Spectroscopic Studies of the Products of the Reaction of Triorganotin(IV) Derivatives with 6-Thiopurine

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Abstract

A structural study of the products of the reaction of R_3Sn^{IV} derivatives (R = Me, Bu^n, Ph) with 6-thiopurine, 6-TPH_2, and its sodium salt, 6-TPHNa, has been undertaken using Mössbauer spectroscopy and the point-charge model rationalization of the Mössbauer parameter nuclear quadrupole splitting. The synthetic reactions have been carried out at *ca.* 0 °C, 20 °C and 50 °C. The Mössbauer spectra of the complexes AlK_3Sn(6-TPH) are consistent with the occurrence of two distinct tin(IV) sites in samples prepared at the lower temperature, while one only site appears by increasing the temperature of the reaction. Two tin sites constantly occur in the products of the reactions involving the Ph_3Sn^{IV} moiety; the stoichiometry is assumed to be $(Ph_3Sn)_3$(6-TPH)(6-TP) for the uniquely-formed complex. Solid state polymeric structures with trigonal bipyramidal environments of the tin atoms and planar SnC_3 skeletons have been proposed. The apical ligand atoms have been assumed to be N, S and N, N in the samples showing two individual tin(IV) sites, and N, N when a single site was present.

Introduction

The complex formation of Me_3Sn^{IV} and Bu_2^n-Sn^{IV} moieties with 6-thiopurine (=6-TPH_2) was recently investigated, and a reaction pathway was proposed involving S-stannylation of 6-TPH_2 followed, at temperatures higher than 40 °C, by S-destannylation and N(3)-stannylation [1]. For Me_3Sn(6-TPH) prepared in boiling acetone, a solid state polymeric structure with N(1)–Sn–N(3) axial bonds and equatorial SnC_3 skeletons in a trigonal bipyramidal environment was proposed, on the basis of infrared and ^{119}Sn Mössbauer studies; the primary Sn–S bond would be stabilized in the octahedral Bu_2^nSn(6-$TPH)_2$ complex through chelation by the purine N(7) atoms [1].

In the context of a research project on the antitumor activity of organotin(IV) derivatives, a series of complexes with 6-TPH_2 was tested against leukaemia P-388 in mice; the complexes included the newly prepared Bu_3^nSn(6-TPH), the derivative $(Ph_3Sn)_3$(6-TPH)(6-TP), and an apparent 1:1 complex Ph_3Sn(6-TPH). These compounds were administered to mice as suspensions in water; thus possible structure (solid state)/activity correlations have been discussed essentially in connection with the Me_3Sn^{IV} and $Bu_2^nSn^{IV}$ complexes [2].

To continue the investigations of the chemical and pharmacological aspects in this field, the following topics have been further studied: (i) the experimental evidence for the electrophilic attack of tin to sulfur as the first step of the reaction of R_3Sn^{IV} moieties with 6-TPH; (ii) the structure and bonding in $Bu_3^nSn^{IV}$ and Ph_3Sn^{IV} complexes; (iii) structure/antitumour activity correlations for the latter complexes. For this purpose, syntheses at various temperatures have been carried out and the nature of the products has been investigated by Mössbauer spectroscopy. The results obtained are reported and discussed in this paper.

Experimental

The organotin(IV) derivatives employed here were Alfa or Fluka products; 6-thiopurine monohydrate, 6-$TPH_2 \cdot H_2O$, was obtained from Fluka. The other reagents and solvents were C. Erba analytical grade. All reagents were purified by recrystallization or distillation according to standard procedures.

The methods of synthesis were as follows:

(I), $T \simeq 50$ °C. R_3SnOH (R = Me or Ph) and anhydrous 6-TPH_2 [1] (from 6-$TPH_2 \cdot H_2O$), in the stoichiometries 1:1 (5 or 10 mmol of each reactant) or 3:2 (15:10 mmol), were added together in about 100 ml of acetone; the mixture was refluxed for *ca.* 2 h, and the products recovered as described previously [1–3].

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(II), $T \simeq 20$ °C. The same procedure was followed, as for (I), except that the reaction mixture was stirred at room temperature. In the cases of 1:1 and 3:2 stoichiometries of the reactants, the products precipitated at room temperature. They were filtered off and dried under vacuum. For 2:1 stoichiometry (Ph_3SnOH 20 mmol and 6-TPH_2 10 mmol), a precipitate was obtained on standing overnight at *ca.* −10 °C, and a second crop was collected after partial evaporation of the filtrate. For 1:2 stoichiometry (Ph_3SnOH 10 mmol and 6-TPH_2 20 mmol) stirring was done for *ca.* 5 h. A yellow solid which was identified as 6-TPH_2 was obtained on standing at room temperature for *ca.* 2 days. The acetone filtrate was then concentrated into a rotary evaporator and subsequently mixed with n-pentane, obtaining a white microcrystalline product.

(III), $T \simeq 20$ °C. 10 mmol of 6-TPHNa were obtained by mixing 6-TPH_2 and Na metal in *ca.* 100 ml of anhydrous MeOH. 10 mmol of Ph_3SnCl in 25 ml of anydrous MeOH were then added dropwise and the solution stirred for *ca.* 3 h at room temperature. On standing overnight at *ca.* −10 °C, a white solid was obtained which was filtered off and dried under vacuum.

(IV), $T \simeq 20$ °C. Bu_3^nSnOMe and 6-TPH_2 were reacted in acetone at room temperature as described elsewhere [2].

(V), $T \simeq 0$ °C. The procedure for (I) was followed, employing acetone cooled at *ca.* 0 °C and stirred for *ca.* 3 h at 0 °C; the precipitate was collected as described above.

(VI), $T \simeq 0$ °C. The same procedure as for (IV), employing acetone cooled at *ca.* 0 °C, and recovering the solid product obtained as usual.

The elemental analyses were undertaken by the Istituto di Chimica Organica, University of Milan; the results for a series of preparations of Ph_3Sn^{IV} complexes are reported in Table I.

The Mössbauer spectra were determined on solid samples of the products, with the apparatus and procedures described elsewhere [1], at liquid N_2 temperature, with a $Ca^{119}SnO_3$ source (10 mCi, Radiochemical Centre, Amersham) moving at room temperature with constant acceleration in a triangular waveform. The measured parameters are reported in Table II. Figure 1 shows two representative spectra involving the fitting by four Lorentzian lineshapes.

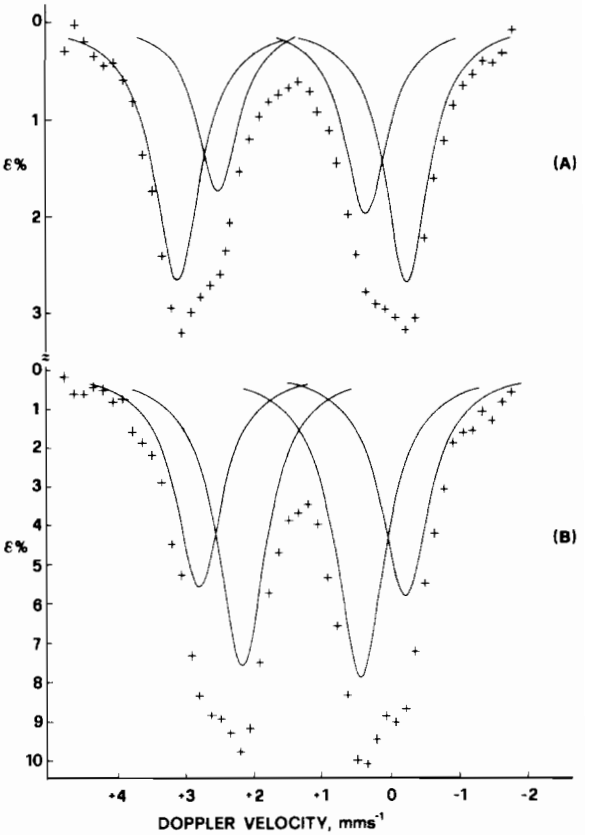

Fig. 1. Examples of four-line Lorentzian fitted spectra. Experimental data points are marked +. (**A**): Bu_3^nSn(6-TPH); (**B**): the product obtained by reaction of Ph_3SnOH with 6-TPH_2; both synthesized at 0 °C by methods (VI) and (III) respectively (see text; Table II, **3** and **5**).

Discussion

The analytical data [1, 2] of the complexes of AlK_3Sn^{IV} moieties undoubtedly suggest 1:1 stoichiometries (Me_3Sn– and Bu_3^nSn–(6-TPH), reaction temperature *ca.* 50 and *ca.* 20 °C, respectively [1, 2]). In the course of the present work, the same stoichiometries have been inferred from the elemental composition determined for samples prepared by methods (II) and (V) (AlK = Me), and (VI) (AlK = Bu^n). For the Ph_3Sn^{IV} complexes, the reaction of $(Ph_3Sn)_2O$ with 6-$TPH_2 \cdot H_2O$ in acetone would generally yield $(Ph_3Sn)_3$(6-TPH)(6-TP) [3]. In fact, the analytical data we determined for a series of products obtained by a number of procedures, partly reported in Table I, do not allow: (i) the unequivocal choice of elemental composition from those assumed as possible (corresponding *i.e.* to 3:2 and 1:1 stoichiometries of the reactants [2, 3]), which would be based essentially on the values of % N, showing the larger difference for the two compositions (Table I); (ii) a satisfactory correlation of the reaction conditions with the possible elemental composition (Table I).

Relevant features of the Mössbauer spectra of the reaction products are as follows:

(i) The experimental resonance absorptions of the AlK_3Sn^{IV} complexes prepared by reactions at *ca.* 0 °C are consistent with either an unresolvable doublet with large Γ values (Table II, code No. **1**) or with four fitting lines which identify an outer

TABLE I. Analytical Data for the Products of the Reactions of Ph_3Sn^{IV} Derivatives with 6-Thiopurine[a].

	Melting point (°C)	Analysis				
		C	H	N	S	Sn
Calculated (%)						
$(Ph_3Sn)_3$(6-TPH)(6-TP), $C_{64}H_{50}N_8S_2Sn_3$		56.88	3.73	8.29	4.75	26.35
Ph_3Sn(6-TPH), $C_{23}H_{18}N_4SSn$		55.12	3.62	11.18	6.40	23.68
Found (%)[b]						
Reaction (method)[c]						
Ph_3SnOH + 6-TPH_2 (I, $T \simeq 50$ °C)	218–19	54.69[d]	3.90[d]	10.50[d]		
Ph_3SnOH + 6-TPH_2 (II, $T \simeq 20$ °C)	218–19	56.20	3.89	8.79		
$3Ph_3SnOH$ + 2(6-TPH_2) (II, $T \simeq 20$ °C)	221–22	56.70	3.76	7.95		
Ph_3SnCl + 6-TPHNa (III, $T \simeq 20$ °C)	222–28	56.79	3.45	6.92		
Ph_3SnOH + 6-TPH_2 (V, $T \simeq 0$ °C)	195–6	54.11	3.71	11.24		

[a]= 6-TPH_2. [b]Average values. [c]See text. Recrystallization was performed for several samples; this did not substantially influence the analytical data reported here. [d]Ref. 2.

TABLE II. Mössbauer Parameters of Complexes of R_3Sn^{IV} with 6-Thiopurine[a], Measured at 77 K.

Code number	Compound, or reaction (method)[b]		δ[c] (mm s^{-1})	ΔE_{exp}[d] (mm s^{-1})	Γ_1[e] (mm s^{-1})	Γ_2[e] (mm s^{-1})	ϵ_1[f] (%)	ϵ_2[f] (%)	Absorber thickness[g]
1	Me_3Sn(6-TPH) (V, $T \simeq 0$ °C)		1.30	2.89	1.32	1.38	2.85	3.04	0.64[h]
2	Me_3Sn(6-TPH) (II, $T \simeq 20$ °C)		1.35	3.21	0.88	0.89	4.08	4.34	0.53[h]
3	Bu_3^nSn(6-TPH) (VI, $T \simeq 0$ °C)	outer inner	1.41 1.42	3.28 2.17	0.83 0.74	0.76 0.77	2.65 1.73	2.69 1.96	0.52[h]
4	Bu_3^nSn(6-TPH) (IV, $T \simeq 20$ °C)		1.50	3.32	1.04	1.06	4.95	4.86	0.62[h]
5	Ph_3SnOH + 6-$TPHI_2$ (V, $T \simeq 0$ °C)	outer inner	1.27 1.28	3.03 1.74	0.84 0.86	0.87 0.88	5.57 7.61	5.86 7.89	66.2[i]
6	Ph_3SnOH + 6-TPH_2 (II, $T \simeq 20$ °C)	outer inner	1.29 1.31	3.01 1.78	0.81 1.08	1.05 0.94	1.61 2.81	2.12 2.43	85.8[i]
7	$3Ph_3SnOH$ + 2(6-TPH_2) (II, $T \simeq 20$ °C)	outer inner	1.27 1.29	2.99 1.74	0.91 0.85	0.87 0.94	2.82 3.13	2.73 3.49	73.0[i]
8	Ph_3SnCl + 6-TPHNa (III, $T \simeq 20$ °C)	outer inner	1.26 1.28	3.03 1.77	0.88 0.90	0.89 0.96	2.69 3.47	3.02 3.81	90.0[i]
9	$2Ph_3SnOH$ + 6-TPH_2 (III, $T \simeq 20$ °C)	outer inner	1.26 1.29	2.99 1.76	0.96 0.93	0.93 0.93	5.01 6.06	5.13 6.67	78.4[i]
10	Ph_3SnOH + 2(6-TPH_2) (III, $T \simeq 20$ °C)	outer inner	1.24 1.28	3.01 1.78	0.87 0.84	0.79 0.84	2.25 5.76	2.05 6.29	7.22[i]
11	Ph_3SnOH + 6-TPH_2 (I, $T \simeq 50$ °C)	outer inner	1.28 1.31	3.05 1.77	0.80 0.78	0.74 0.84	2.75 3.26	2.53 3.91	81.2[i]
12	$3Ph_3SnOH$ + 2(6-TPH_2) (I, $T \simeq 50$ °C)	outer inner	1.27 1.30	3.05 1.75	0.81 0.84	0.82 0.84	3.10 3.96	3.13 4.11	98.1[i]

[a]= 6-TPH_2. [b]See text, and Table I for the nature of the products involving Ph_3Sn^{IV} species. [c]Isomer shift with respect to room temperature $Ca^{119}SnO_3$. [d]Experimental nuclear quadrupole splitting. [c,d]Data are generally average values from the spectra of a number of samples obtained from a series of synthetic batches. Outer and inner refer to outer and inner Lorentzian fitted doublets. [e]Full width at half height of the Lorentzian fits of the resonant peaks. [f]Per cent resonance effect at the maximum. [e,f,g]Data refer to the given absorber sample. [h]mg $^{119}Sn/cm^2$. [i]mg of product/cm^2.

(with a larger $\epsilon\%$) and an inner doublet (Table II, No. **3**, and Fig. 1(A)). When the reaction temperature is raised, the inner doublet disappears, and spectra consisting of two reasonably narrow resonant lines (Table II, Nos. **2** and **4**) are obtained.

(ii) The experimental spectra of the Ph_3Sn^{IV} complexes are generally fitted by four Lorentzian lineshapes describing an outer doublet (with a less $\epsilon\%$) and an inner one, irrespective of the synthetic reaction conditions. The ratios of $\epsilon\%$ at the resonance maxima of inner-to-outer lines, as well as of the respective areas under the resonance peaks ($A = \frac{\pi}{2} \times \epsilon \times \Gamma$), are also essentially constant (see e.g. Table II, Nos. **5–9**, **11**, **12**, and Fig. 1 (B)).

The trends shown by the Mössbauer spectra clearly suggest that: (i) the reaction of AlK_3Sn^{IV} with 6-TPH_2 occurs via an intermediate product which is present in the samples prepared at *ca.* 0 °C; (ii) the reactions of Ph_3Sn^{IV} derivatives with 6-TPH_2 and 6-TPHNa generally yield a unique product.

The nature of bonding and configuration at the tin sites, as evidenced by the Mössbauer spectra, may be extracted from the point-charge model rationalization of the nuclear quadrupole splitting parameters [1, 4]. The ΔE_{exp} values of the outer doublets of compounds **3**, **5–12**, Table II, are fully consistent with the trigonal bipyramidal structure (A), Fig. 2, due to their excellent agreement with the related point-charge model estimate, ΔE_{calc}; the same holds for the two-line spectra of compounds Nos. **2** and **4**, Table II. Among other trigonal bipyramidal tin sites, possibly occurring in the present context [5], the isomer with meridional SnC_3 and equatorial N, N ($\Delta E_{calc} = -3.67$ [5]) could be assumed for the $Bu_3{}^nSn^{IV}$ complexes (Nos. **3** and **4**, Table II). The same would also hold for the isomer with meridional SnC_3 and equatorial N, S in connection with the complexes of Me_3Sn^{IV} and Ph_3Sn^{IV} ($\Delta E_{calc} = -2.91$ [5] and -2.74, respectively; Nos. **2**, **5–12**, Table II). On the other hand, in view of larger differences $|\Delta E_{exp}| - |\Delta E_{calc}|$ (the maximum accepted value being 0.4 mm s^{-1} [1]), these attributions seem less acceptable than structure (A).

For the site inherent to the inner doublets, ΔE_{exp} values of Nos. **3**, **5–12**, Table II, fully agree with ΔE_{calc} for structure (**B**), Fig. 2. Isomers with facial SnC_3, axial S and equatorial N for the $Bu_3{}^nSn^{IV}$ complex ($\Delta E_{calc} = -2.41$ [5]), as well as axial and equatorial N, N for both $Bu_3{}^nSn^{IV}$ and Ph_3Sn^{IV} derivatives ($\Delta E_{calc} = +2.22$ [5] and -1.95, respectively) cannot be excluded primarily on the above grounds. Tetrahedral tin sites are highly improbable (e.g., ΔE_{calc} for tetrahedral AlK_3SnSPh and Ph_3SnSPh are -1.64 and -1.42, respectively [6]).

If tin sites of type (**A**), Fig. 2, are attributed to the outer doublets and to two-line spectra, and the sites of type (**B**) to inner doublets, in line with the preceding discussion, it could be concluded that the proposed reaction mechanism, involving the primary attack of 6-thiopurine sulfur [1], does actually occur, and that AlK_3Sn^{IV} complexes prepared at temperatures larger than 0 °C actually show the solid state polymeric trigonal bipyramidal structure with apical N, N previously advanced for the Me_3Sn^{IV} derivative [1]. Moreover, if the stoichiometry $(Ph_3Sn)_3$(6-TPH)(6-TP) [3] is assumed for the uniquely-formed Ph_3Sn^{IV} complex (*vide supra*), its structure could consist of the solid state polymer depicted in Fig. 3; this could be caused by the lack of S-destannylation of these complexes at high temperature, in contrast to what occurs for the AlK_3Sn^{IV} complexes [1].

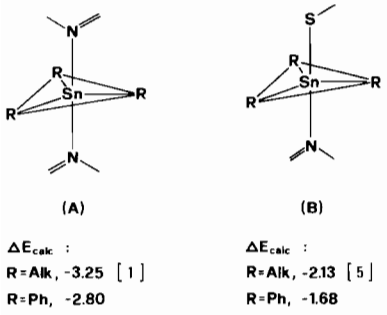

Fig. 2. Possible tin environments in R_3Sn^{IV} complexes with 6-TPH_2, and the corresponding nuclear quadrupole splitting values calculated by the point-charge model formalism, ΔE_{calc}, mm s^{-1} (see text). Symbols S and N stand for donor atoms of coordinated 6-thiopurine.

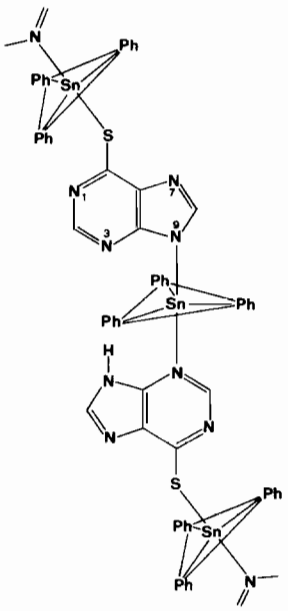

Fig. 3. A possible structure of the complex $(Ph_3Sn)_3$(6-TPH)(6-TP), as inferred from the Mössbauer parameters (this work) and IR and NMR data [3]. The coordinate bond N–Sn could in principle involve any of the N(1), N(3) or N(7) atoms of 6-thiopurine (undctermined on the basis of the presently available results).

The latter effect could be tentatively interpreted in terms of a higher orbital electronegativity of tin in the Ph_3Sn^{IV} moiety, which would strengthen the Sn–S bond. Lastly, the previously-discussed correlation between anti-leukaemia activity and structure [2] also appears to apply for the complexes investigated here.

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